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Please note that this annual report is for a project with three principal investigators: Michael Jarstfer, Cort Pedersen, and Sheryl Moy.
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14. ABSTRACT
Currently, there are no established pharmaceutical strategies that effectively treat core autism spectrum disorder (ASD) symptoms, including pervasive social deficits and repetitive behaviors. The oxytocin pathway has an important role in normal human social behaviors, and oxytocin dysregulation has been implicated in ASD-associated behavioral symptoms. There is now emerging evidence that oxytocin has therapeutic efficacy in ameliorating core ASD symptoms associated with social behavior. However, from the standpoint of drug discovery, oxytocin is a poor candidate as a standard clinical treatment. Oxytocin is rapidly metabolized and has low brain penetrance with peripheral administration. The goal of the proposed studies is to discover new small-molecule compounds that enhance oxytocin signaling, as novel drug interventions for social deficits and abnormal repetitive behavior relevant to ASD. In this third year, we have extended our published findings that oxytocin can effectively overcome representative ASD phenotypes in two mouse lines that model ASD-like behaviors, including overt alterations in social behavior, and we have confirmed these effects in a genetic model of social impairment, the *Grin1* knockdown mouse. We have also evaluated one synthetic oxytocin agonist, Compound 39, and one oxytocin metabolite, for efficacy against social deficits in BALB/cByJ mice, and we are currently evaluating a second oxytocin metabolite for prosocial effects. Overall, we have successfully validated three mouse models for as preclinical screens for compounds targeting the oxytocin receptor, and provided leads for a drug discovery campaign for social deficits and other core autism symptoms.

15. SUBJECT TERMS
autism, mouse model, neuropeptides, oxytocin, sociability

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Introduction

Currently, there are no established pharmaceutical strategies that effectively treat core autism spectrum disorder (ASD) symptoms, including pervasive social deficits and repetitive behaviors. The oxytocin pathway has an important role in normal human social behaviors, and oxytocin dysregulation has been implicated in ASD-associated behavioral symptoms. There is now emerging evidence that oxytocin has therapeutic efficacy in ameliorating core ASD symptoms associated with social behavior. However, from the standpoint of drug discovery, oxytocin is a poor candidate as a standard clinical treatment. Oxytocin is rapidly metabolized and has low brain penetrance with peripheral administration. The goal of the proposed studies is to discover new small-molecule compounds that enhance oxytocin signaling, as novel drug interventions for social deficits and abnormal repetitive behavior relevant to ASD. In the first three years of our project, we have established that oxytocin can effectively overcome representative ASD phenotypes in three mouse lines that model ASD-like behaviors, including overt alterations in social behavior and abnormal repetitive behavior. We are currently prioritizing synthetic compounds that activate the oxytocin receptor using cell-based assays, and evaluating the therapeutic efficacy of the top molecules in the characterized mouse lines (presently, compound 39 and the oxytocin derivatives OT(4-9) and OT (5-9)). Our research employs a highly-innovative screening paradigm to identify activators of oxytocin function relevant to treatment strategies for ASD. The successful completion of the proposed aims will validate the oxytocin pathway as a drug target for the amelioration of ASD-associated phenotypes, contribute to the drug discovery process by establishing mouse models for preclinical testing, and provide leads for a drug discovery campaign directed at the oxytocin receptor.

Body

Validation of mouse models as preclinical efficacy screens. We have previously observed low sociability in adolescent mice from the BALB/cByJ (Moy *et al*, 2007) and C58/J (Moy *et al*, 2008; Ryan *et al*, 2010) inbred strains and in the *Grin1* knockdown mouse (Duncan et al. 2004; Moy et al. 2012). . In year two of this DoD award, we published a manuscript reporting that the lack of social preference in both the BALB/cByJ and C58/J models can be reversed by a 2-week chronic regimen of oxytocin (1.0 mg/kg) treatment (Teng *et al*, 2013), whereas a single dose of oxytocin was ineffective. Our findings are the first evidence that the two inbred strain models can be utilized as preclinical screens for prosocial effects of novel compounds active at the oxytocin receptor. A particularly intriguing aspect of our findings in the BALB/cByJ mice is that prosocial effects of oxytocin can be observed 24 hours after the final oxytocin treatment. More recently, we have determined that enhanced sociability is still strongly present 48 hours following oxytocin treatment (Figure 1A,D). In this project, we also proposed to evaluate a genetic mouse model of autism-like phenotypes, the *Grin1* knockdown mouse. The *Grin1* gene encodes the NR1 subunit of the NMDA receptor. In the third year of the project, we have confirmed and extended our previous findings to show that social deficits are rescued in male BALB/cByJ, C58/J, and *Grin1* knockdown models including the remarkable observation that the rescue is persistent 14 days following oxytocin treatment in adult C58/J male mice (**Figure 1**), as well as adolescent C58/J mice (Teng et al. 2013).

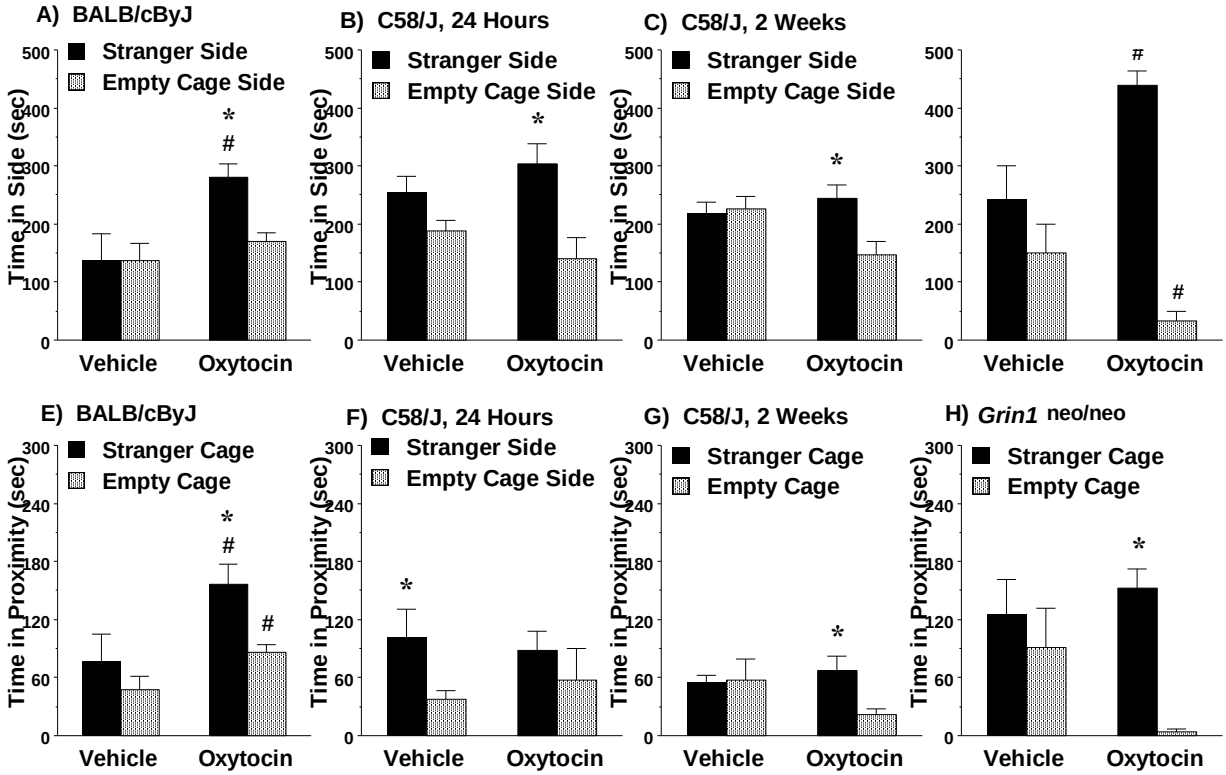


Figure 1. Prosocial effects of oxytocin in BALB/cByJ, C58/J, and *Grin1*$^{neo/neo}$ male mice. Subjects were tested for sociability in a 3-chamber choice task. The subchronic regimen consisted of 4 treatments with either vehicle or oxytocin (IP; 1.0 mg/kg) across an 8-9 day period, with at least 48 hr between each injection. BALB/cByJ was tested 48 hr following the final treatment; C58/J was tested at 24 hr, and again at 2 wk, following the final treatment; and *Grin1* knockdown (*Grin1*$^{neo/neo}$) mice were tested 24 hr following the final treatment. *p<0.05, within-group comparison to empty cage side. #p<0.05, comparison to vehicle-treated group.

Prosocial oxytocin effects in adult C58/J female mice. Female mice treated with oxytocin demonstrated significant preference for the stranger side when tested 24 hours (**Figure 2A**), but not 2 weeks (**Figure 2D**), following the end of the subchronic regimen [within-treatment group post-hoc analyses following significant effect of side, $F(1,13)=11.40$, $p=0.005$]. Significant preference for proximity to the stranger cage was observed at both time points in the oxytocin-treated groups, but not the vehicle-treated groups (**Figure 2B**, **E**) [effect of side, $F(1,13)=34.29$, $p<0.0001$]. There were no significant effects of treatment or side on number of entries during the test (**Figure 2C**, **F**).

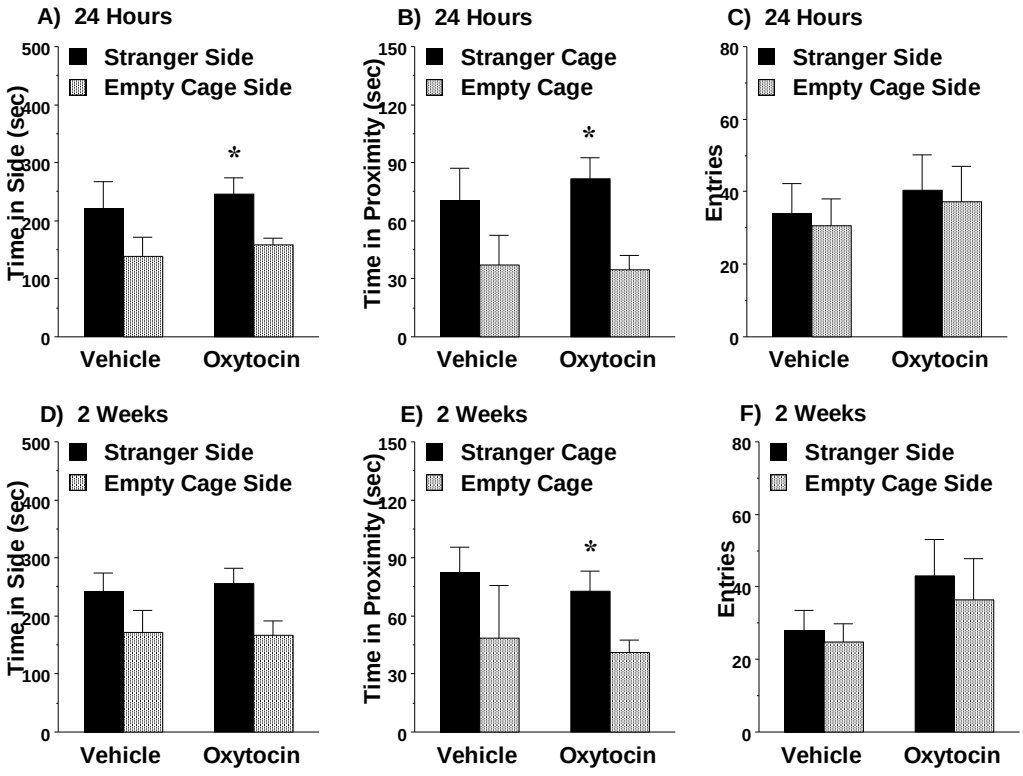


Figure 2. Prosocial effects of oxytocin in C58/J female mice. Significant social preference was only observed in the group treated with oxytocin. The subchronic regimen consisted of 4 treatments with either vehicle or oxytocin (IP; 1.0 mg/kg) across an 8-9 day period, with at least 48 hr between each injection. Mice were tested at 24 hr, and again at 2 wk, following the final treatment. *$p<0.05$, within-group comparison to empty cage side.

Prioritization of positive allosteric modulators and agonists. We previously completed a high throughput screen of over 300,000 compounds in order to identify compounds that activate the oxytocin receptor. All initial positive agonists (199 compounds) and allosteric modulators (65 compounds) have been confirmed using fluorescence-based assays. Overall, most agonists were moderately potent (EC_{50} ranged from 5 to 100 μM). However, agonists displayed little selectivity for the oxytocin receptor when compared to vasopressin receptors. These results were validated with Ca^{2+} release assays as well as IP_3 formation assays (data not shown). We have examined several series of analogs based on active hits, but have not achieved increased specificity. To further our efforts towards new oxytocin (OT) receptor agonists, we examined several oxytocin fragments expected to be metabolites of oxytocin, which we consider derivatives of an active hit from the high throughput screen per Task 5. In year two we reported that these fragments do not have activity against human orphan receptors. We have now tested these OT derivatives against the OT receptor using a "Tango" assay. Surprisingly, even though OT(4—9) exhibited OT activity in vivo, it did not demonstrate OT activity in this cell based assay.

Allosteric modulators, which are more desirable, were generally less potent with maximum increase in response to oxytocin typically about 10 percent. In order to optimize potency, we have continued exploring analoging of derivatives in order to optimize their activity. To date, we have screened 69 analogs of three initial hits (a functionalized amino acid, a pyrazolopyrimidine, and a triazole) in the positive allosteric modulator assay. In year three, we assayed the triazole analogs (**Figure 3**). The data revealed that even at high concentrations, unfortunately analogs of these three initial hits are not potent enough to warrant further analysis.

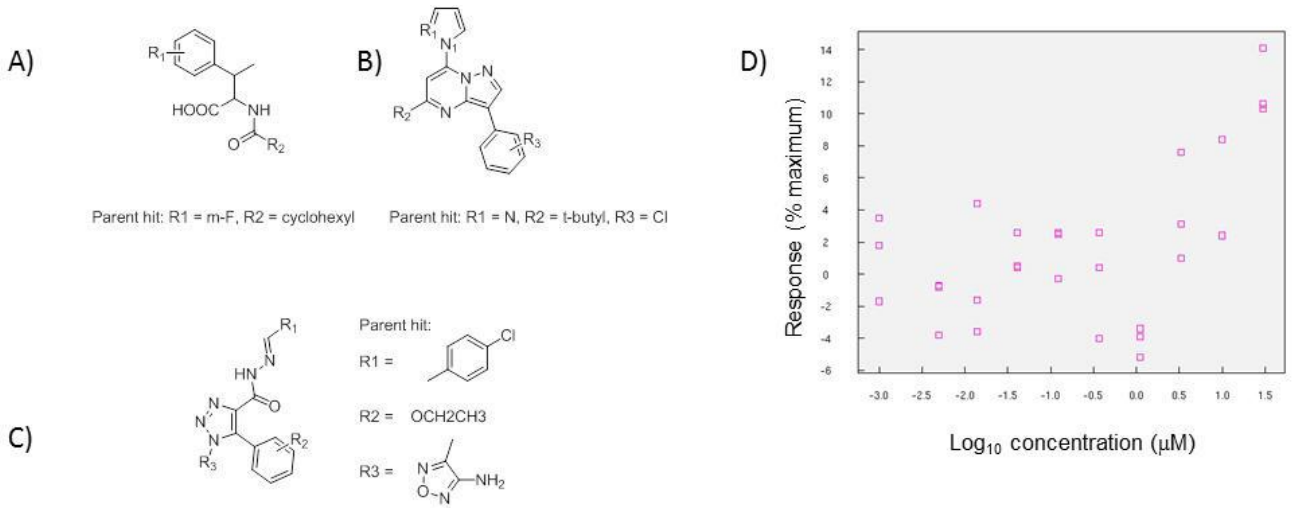
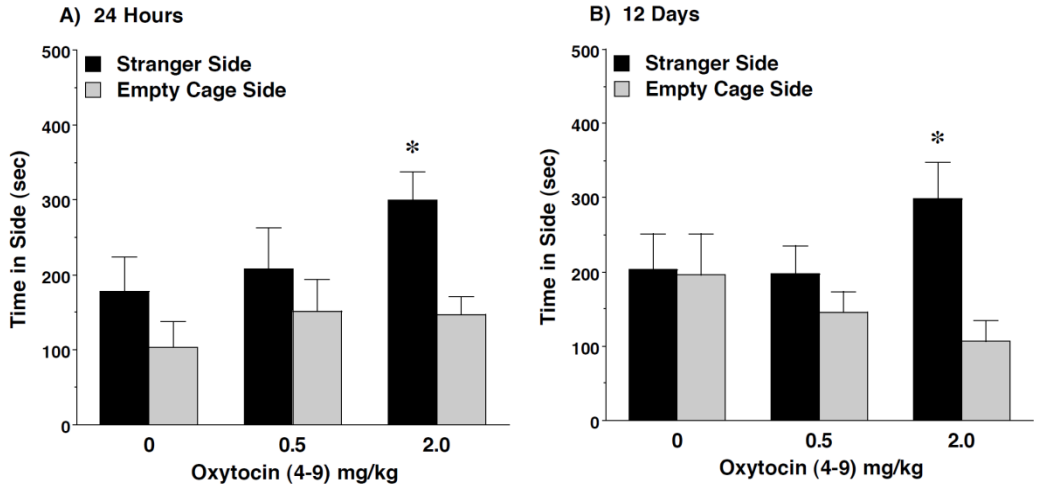


Figure 3. Analysis of positive allosteric modulators of the human oxytocin receptor. Three series of analogs based on initial hits from our high throughput screen for positive allosteric modulation of the human oxytocin receptor have been analyzed. (A) Amino acid derivatives tested in year one. (B) Pyrazolopyrimidine derivatives tested in year two. (C) Triazoles substituted with heteroaromatic rings were tested in year three. Example dose response for the triazole derivatives, the parent compound, in an allosteric modulator assay. The data did not fit to the Hill equation. In short, CHO cells stably transfected with the oxytocin receptor were treated with test compound and 1 nM oxytocin and the oxytocin receptor response was detected by calcium accumulation. Triplicate data were fit by nonlinear regression.

Plans for prioritization of positive allosteric modulators and agonists. In year three, we examined analogs from 1 positive allosteric modulator (PAM) series. In total now, we have examined analogs based on ten hits from our initial screen. We have determined that PAM design will require an alternative approach and agonist develop will focus on the OT derivatives and beta-arrestin selectivity. .

Establish the effects of OT(4-9) on the behavior of ASD-model mice.

In last years report, we showed that sub-chronic treatment regimens with either the higher or lower dose of Compound 39, , a synthetic oxytocin agonist failed to rescue social deficits in the BALB mice (**not shown**). However, we observed that sub-chronic treatment with the oxytocin (4-9) metabolite led to significant increases in social preference (Figure 4), suggesting that fragments of the oxytocin nonapeptide might have full prosocial potency. In the third year, we focused much of our attention on OT(4-9) as it represents a new chemical entity with pro-social effects. We confirmed that OT(4-9) exhibits dose-dependent and persistent prosocial effects in BALB mice (**Figure 4).**



Persistent prosocial effects of oxytocin fragment (4-9) in BALB/cByJ. Vehicle or oxytocin (4-9) was administered across an 8-9 day period. Subjects given 2 tests in a three-chambered choice task, one 24 hours and one 12 days following the final dose. The 24-hour test was conducted with a photobeam-based system, and the 12-day test was conducted with an automated tracking system. There were no significant effects of treatment or side on entries during either test. N=8 male, adolescent mice per group. *p<0.05, within-treatment comparison.

Key Research Accomplishments

1. Confirmed that sub-chronic oxytocin treatment has highly significant prosocial effects in *Grin1* knockdown mice, a genetic model of glutamatergic hypofunction.
2. Characterized OT(4-9) activity in the BALB/cByJ mouse model.
3. Evaluated derivatives of initial positive allosteric modulator hit in cell-based assays.
4. Key accomplishments in relationship to proposed Statement of Work: we have completed subtasks 1a, 1b, 1c, 1d., 2a, 2b, 2c,2d, 3a, 3b, 3c, 3d (one published manuscript and another is in preparation), 4a, 4b, and initiated 5a, 5b, 6a-6e (see appendix for proposed Statement of Work).

Reportable Outcomes

1. The research team, including Dr. Brian Teng, the post-doctoral fellow recruited for this project, have published a manuscript on the validation of two mouse models as screens for oxytocin effects on social deficits and repetitive behavior (**Appendix II**).
2. The results of the our research, including the synthetic oxytocin receptor agonist Compound 39, were presented at the International Meeting for Autism Research May 2-4, 2013. The full abstract is in Appendix II.

Conclusion

In the first 34 months of the funded project, we have made significant progress, particularly on validating our proposed mouse models and in determining the ability of non-peptide synthetic compounds to affect the oxytocin receptor and the identification of two derivatives with oxytocinergic activity in sociability assays. We demonstrated that oxytocin can reverse social deficits in C58/J, BALB/cByJ and *Grin1* knockdown mice. Most remarkably, we showed that, in each case, chronic oxytocin treatment was required to promote prosocial activity. This is an important observation that will inform both preclinical screening, as well as clinical trials. Prosocial effects were persistent for 48 hours in BALB/cByJ mice, and two weeks following treatment in the C58/J mice. The results with the mouse models indicate that oxytocin treatment results in molecular changes that are more complex and long lasting than simply activating the oxytocin receptor.

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Teng BL, Nonneman RJ, Agster KL, Nikolova VD, Davis TT, Riddick NV, *et al* (2013). Prosocial effects of oxytocin in two mouse models of autism spectrum disorders. *Neuropharmacology* **72**: 187-196.

Appendix I

Statement of Work

NOTE: There is one animal site for all experiments: the Mouse Behavioral Phenotyping Laboratory, the corresponding PI is Sheryl Moy, though each PI will participate in experimental design and data interpretation.

Task 1. Establish the effect of oxytocin on the behavior of *Grin1*$^{neo/neo}$ mice (Major contribution from Drs. Moy and Pedersen, minor contribution from Dr Jarstfer). **Performance site: UNC Chapel Hill, Mouse Behavioral Phenotyping Laboratory, Medical Biomolecular Research Building.**

Number of mice: 183

Subtask 1a. Submit forms for IACUC approval of animal studies (month 1).

Subtask 1b. Submit ACURO Animal Use Appendix for Research Involving Animals documents for review and approval of animal studies (months 1-4).

Subtask 1c. Rear and genotype *Grin1*$^{neo/neo}$ mice and wild type controls (months 4-36).

Subtask 1d. Test the effect of oxytocin on the behavior of *Grin1*$^{neo/neo}$ mice in the social approach test (months 6-12). The social approach test uses an automated apparatus for quantitation of social approach behaviors (as described in Moy et al., *Genes, Brain and Behavior* (2004) 3: 303–314). In short, time spent in each chamber and the number of entries are scored automatically by a system detecting photocell beam breaks. We also measure time sniffing and sniffing bouts.

Task 2. Establish the effect of oxytocin on the behavior of C58/J mice. (Major contribution from Drs. Moy and Pedersen, minor contribution from Dr Jarstfer). **Performance site: UNC Chapel Hill, Mouse Behavioral Phenotyping Laboratory, Medical Biomolecular Research Building.**

Number of mice: 143

Subtask 2a. Submit forms for IACUC approval of animal studies (month 1).

Subtask 2b. Submit ACURO Animal Use Appendix for Research Involving Animals documents for review and approval of animal studies (months 1-4).

Subtask 2c. Test the effect of oxytocin on the behavior of C58/J mice in the social approach test (months 6-12).

Subtask 2d. Test the effect of oxytocin on the behavior of C58/J mice in the repetitive behavior test (months 12-18).

Task 3. Establish the effect of oxytocin on the behavior of BALB/cByJ mice. (Major contribution from Drs. Moy and Pedersen, minor contribution from Dr Jarstfer). **Performance site: UNC Chapel Hill**

Mouse Behavioral Phenotyping Laboratory, Medical Biomolecular Research Building

Number of mice: 84

Subtask 3a. Submit forms for IACUC approval of animal studies (month 1).

Subtask 3b. Submit ACURO Animal Use Appendix for Research Involving Animals documents for review and approval of animal studies (months 1-4).

Subtask 3c. Test the effect of oxytocin on the behavior of BALB/cByJ mice in the social approach test (months 6-12).

Subtask 3d. Publish findings from tasks 1-3 in scholarly journal.

Task 4. Validate active compounds from the high throughput screen. (Major contribution from Jarstfer). **Performance sites: UNC Chapel Hill Genetics Medicine Building (FLIPR assays) and Beard Hall (data analysis and interpretation).**

Subtask 4a. Confirm and characterize active agonists from the initial high throughput screen using resynthesized compounds (months 1-4)

Subtask 4b. Confirm and characterize active positive allosteric modulators from the initial high throughput screen using resynthesized compounds (months 2-5)

Task 5. Identify lead compounds for testing in animal models. (Major contribution from Jarstfer).

Performance site: UNC Chapel Hill, Genetic Medicine building.

For Task 5, the Specialized Chemistry Center for Accelerated Probe Development will perform synthesis of compounds based on the activity we observe in our cell-based assays. They will perform a service – both intellectually and physically – by making molecules and determining potential derivatives to optimize activity. No cell-based or animal assays will be conducted at the Center. In Task 4, the compounds are the initial hits from the high throughput screen. In Task 5, the compounds are derivatives of the hits, either synthetic or commercially available compounds.

Subtask 5a. Conduct iterative syntheses and testing of agonists in collaboration with the Vanderbilt Specialized Chemistry Center for Accelerated Probe Development (months 4-24). We will test between 50 and 200 compounds.

Screening will be conducted using first the cell-based calcium release assay we used in the HTS. Positives will be further analyzed using IP3 release assays. Counter assays using untransfected cells and cells expression the vasopressin receptor will confirm selectivity.

Subtask 5b. Conduct iterative syntheses and testing of positive allosteric modulators in collaboration with the Vanderbilt Specialized Chemistry Center for Accelerated Probe Development (months 5-24).

We will test between 50 and 200 compounds.

Screening will be conducted using first the cell-based calcium release assay we used in the HTS. Unlike the agonist assay, these assays will include a low level of oxytocin to prime the receptor. Positives will be further analyzed using IP3 release assays. Counter assays using untransfected cells and cells expression the vasopressin receptor will confirm selectivity.

Subtask 5c. Analysis of safety and untoward activity of potential test compounds (Months 18-28). Compounds will be screened in cell based assays for activity against other receptors. In particular, assays for bioavailability predictions (CaCo2, MDR-1) and cardiovascular toxicity predictions (HERG, 5-HT2B) will be conducted.

Subtask 5d. Publish identification of new oxytocin receptor agonists and positive allosteric modulators.

Task 6. Establish the effect of small molecule agonists on the behavior of ASD-model mice (Major contribution from Drs. Moy and Pedersen, minor contribution from Dr Jarstfer). **Performance site: UNC Chapel Hill Mouse Behavioral Phenotyping Laboratory, Medical Biomolecular Research Building**

Agonists will be tested without the addition of oxytocin. Endogenous oxytocin will be present at endogenous levels, but we will not add addition oxytocin.

Subtask 6a. Determine appropriate dose of test compounds in C57BL/6J mice using acoustic startle test (months 18-24).

Subtask 6b. Test the effect of target compounds on the behavior of *Grin1*$^{neo/neo}$ mice in the social approach test (months 24-36).

Subtask 6c. Test the effect of target compounds on the behavior of C58/J mice in the social approach test (months 24-36).

Subtask 6d. Test the effect of target compounds on the behavior of C58/J mice in the repetitive behavior test (months 24-36).

Subtask 6e. Test the effect of target compounds on the behavior of BALB/cByJ mice in the social approach test (months 24-36).

Appendix II

International Meeting for Autism Research abstract

Mouse Models of Autism Phenotypes As Preclinical Screening Platforms for Novel Oxytocinergic Compounds

B. L. Teng1,2, R. J. Nonneman1,3, V. D. Nikolova1,4, K. L. Agster1,4, T. T. Davis1,2, N. V. Riddick1,4, L. K. Baker1, C. A. Pedersen1,4, M. B. Jarstfer1,2 and S. S. Moy1,4,

(1)Carolina Institute for Developmental Disabilities, University of North Carolina School of Medicine, Chapel Hill, NC, (2)UNC Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC, (3)Department of Genetics, University of North Carolina School of Medicine, Chapel Hill, NC, (4)Department of Psychiatry, University of North Carolina School of Medicine, Chapel Hill, NC

Background: There is emerging evidence that oxytocin (OT) treatment can improve social deficits and repetitive behavior in autism spectrum disorders (ASDs). However, administration of the neuropeptide, which has a short plasma half-life and poor ability to penetrate the blood-brain barrier, is a problematic issue for clinical use. We have recently initiated a drug development program to identify novel, highly selective, non-peptide OT receptor (OTR) agonists. These efforts would be accelerated by animal models to screen drug candidates for efficacy against ASD-relevant phenotypes.

Objectives: Validate mouse models for preclinical screening of compounds that target the OT pathway, in order to facilitate the development of therapeutics for core ASD symptoms. Methods: BALB/cByJ and C58/J are well-characterized inbred mouse strains that exhibit behavioral phenotypes relevant to ASD. To validate these models as preclinical screens, mice were tested for OT effects on sociability in a three-chamber task and perseverative responses in a marble-burying assay. C58/J was also examined for OT effects on repetitive behavior and open field activity. These screening platforms were then used to evaluate Compound 39 (a synthetic, non-peptide OTR agonist).

Results: The acute OT regimen did not increase sociability in BALB/cByJ. However, the sub-chronic OT regimen (i.e. four intraperitoneal injections across 7-8 days) had significant prosocial effects in both BALB/cByJ and C58/J. Increased sociability was observed 24 hr following the final OT dose in BALB/cByJ, while prosocial effects of OT emerged 1-2 weeks post-treatment in C58/J. An acute OT regimen decreased motor stereotypy in C58/J, at a dose that did not produce sedative or anxiolytic-like effects in open field testing. Similarly, acute OT treatment led to significant reductions in marble-burying by BALB/cByJ. Consistent with previous research, Compound 39 produced some OT-like effects; however, the drug had no effect on sociability.

Conclusions: These studies show that OT reverses social deficits in mouse models of ASD, dependent on dose regimen and genotype. Furthermore, acute OT decreases abnormal repetitive behavior in C58/J and marble-burying in BALB/cByJ. These findings provide validation of the BALB/cByJ and C58/J models as valuable platforms for screening novel drugs for intervention in ASDs, and for elucidating the mechanisms contributing to prosocial and other beneficial effects of OT.

Publication from work.

Teng, B.L., Nonneman, R.J., Agster, K.L., Nikolova, V.D., Davis, T.T., Riddick, N.V., Baker, L.K., Pedersen, C.A., Jarstfer, M.B., Moy, S.S. (2013) Prosocial effects of oxytocin in two mouse models of autism spectrum disorders. *Neuropharmacology* **72**: 187-196.